



RIFM fragrance ingredient safety assessment, propyl isovalerate, CAS Registry Number 557-00-6

A.M. Api^a, D. Belsito^b, D. Botelho^a, M. Bruze^c, G.A. Burton Jr.^d, M.A. Cancellieri^a, H. Chon^a, M.L. Dagli^e, M. Date^a, W. Dekant^f, C. Deodhar^a, A.D. Fryer^g, L. Jones^a, K. Joshi^a, M. Kumar^a, A. Lapczynski^a, M. Lavelle^a, I. Lee^a, D.C. Liebler^h, H. Moustakas^a, M. Na^a, T.M. Penningⁱ, G. Ritacco^a, J. Romine^a, N. Sadekar^a, T.W. Schultz^j, D. Selechnik^a, F. Siddiqi^a, I.G. Sipes^k, G. Sullivan^{a,*}, Y. Thakkar^a, Y. Tokura^l

^a Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA

^b Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA

^c Member Expert Panel for Fragrance Safety, Malmö University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmö, SE-20502, Sweden

^d Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 48109, USA

^e Member Expert Panel for Fragrance Safety, University of São Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, São Paulo, CEP 05508-900, Brazil

^f Member Expert Panel for Fragrance Safety, University of Würzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany

^g Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA

^h Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA

ⁱ Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA

^j Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA

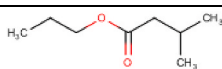
^k Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA

^l Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan

ARTICLE INFO

Handling editor: Dr. Jose Luis Domingo

Version: 120921. Initial publication. This version replaces any previous versions. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



(continued)

Name: Propyl isovalerate

CAS Registry Number: 557-00-6

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

(continued on next page)

(continued on next column)

* Corresponding author.

E-mail address: gsullivan@rifm.org (G. Sullivan).

<https://doi.org/10.1016/j.fct.2022.113120>

Received 9 December 2021; Received in revised form 21 April 2022; Accepted 4 May 2022

Available online 9 May 2022

0278-6915/© 2022 Elsevier Ltd. All rights reserved.

(continued)

CNIH – Confirmation of No Induction in Humans test. A Confirmation of No Induction in Humans test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)

CreME RIFM Model - The CreME RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach

DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

DRF - Dose Range Finding

DST - Dermal Sensitization Threshold

ECHA - European Chemicals Agency

ECOSAR - Ecological Structure-Activity Relationships Predictive Model

EU - Europe/European Union

GLP - Good Laboratory Practice

IFRA - The International Fragrance Association

LOEL - Lowest Observed Effect Level

MOE - Margin of Exposure

MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition

NA - North America

NESIL - No Expected Sensitization Induction Level

NOAEC - No Observed Adverse Effect Concentration

NOAEL - No Observed Adverse Effect Level

NOEC - No Observed Effect Concentration

NOEL - No Observed Effect Level

OECD - Organisation for Economic Co-operation and Development

OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines

PBT - Persistent, Bioaccumulative, and Toxic

PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration

Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.

QRA - Quantitative Risk Assessment

QSAR - Quantitative Structure-Activity Relationship

REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals

RfD - Reference Dose

RIFM - Research Institute for Fragrance Materials

RQ - Risk Quotient

Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test

TTC - Threshold of Toxicological Concern

UV/Vis spectra - Ultraviolet/Visible spectra

VCF - Volatile Compounds in Food

VoU - Volume of Use

vPvB - (very) Persistent, (very) Bioaccumulative

WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

Propyl isovalerate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl 2-methylbutyrate (CAS # 7452-79-1) show that propyl isovalerate is not expected to be genotoxic and provide a Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data from analog hexyl 2-methylbutyrate (CAS

(continued on next column)

(continued)

10032-15-2) provided propyl isovalerate a No Expected Sensitization Induction Level (NESIL) of $7000 \mu\text{g}/\text{cm}^2$ for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; propyl isovalerate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; propyl isovalerate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, propyl isovalerate was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2000a; RIFM, 2014)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day. (ECHA REACH Dossier: Ethyl 2-Methylbutyrate; ECHA, 2013)
Reproductive Toxicity: Developmental toxicity NOAEL: 1000 mg/kg/day. Fertility NOAEL: 1000 mg/kg/day. (ECHA REACH Dossier: Ethyl 2-Methylbutyrate; ECHA, 2013)
Skin Sensitization: NESIL = $7000 \mu\text{g}/\text{cm}^2$. RIFM (2018)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.02 (BIOWIN) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 30.54 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Not applicable
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: not applicable; no Volume of Use in 2015 reported for Europe and North America

1. Identification

1. **Chemical Name:** Propyl isovalerate
2. **CAS Registry Number:** 557-00-6
3. **Synonyms:** Butanoic acid, 3-methyl-, propyl ester; Propyl isopentanoate; Propyl isovalerianate; Propyl 3-methylbutanoate; Propyl 3-methylbutyrate; Propyl isovalerate
4. **Molecular Formula:** $\text{C}_8\text{H}_{16}\text{O}_2$
5. **Molecular Weight:** 144.21 g/mol
6. **RIFM Number:** 6794
7. **Stereochemistry:** No stereocenter possible

2. Physical data

1. **Boiling Point:** 156°C (Fragrance Materials Association [FMA]), 157.09°C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log Kow:** 2.76 (EPI Suite)
4. **Melting Point:** 43.92°C (EPI Suite)
5. **Water Solubility:** 356.7 mg/L (EPI Suite)
6. **Specific Gravity:** 0.86 (FMA)
7. **Vapor Pressure:** 2.18 mm Hg at 20°C (EPI Suite v4.0), 3.05 mm Hg at 25°C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark ($1000 \text{ L mol}^{-1} \text{ cm}^{-1}$)
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95th Percentile Concentration in Air Fresh Plugin:** 0.00028% (RIFM, 2021)
(No Reported use in Fine Fragrance)
2. **Inhalation Exposure*:** 0.000015 mg/kg/day or 0.00096 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.000064 mg/kg/day (RIFM, 2021)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:

- a. **Genotoxicity:** Ethyl 2-methylbutyrate (CAS # 7452-79-1)
- b. **Repeated Dose Toxicity:** Ethyl 2-methylbutyrate (CAS # 7452-79-1)
- c. **Reproductive Toxicity:** Ethyl 2-methylbutyrate (CAS # 7452-79-1)
- d. **Skin Sensitization:** Hexyl 2-methylbutyrate (CAS # 10032-15-2)
- e. **Phototoxicity/Photoallergenicity:** None
- f. **Local Respiratory Toxicity:** None
- g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

Additional References: None.

8. Natural occurrence

Propyl isovalerate is reported to occur in the following foods by the VCF*:

Artocarpus species	Cheese, various types
Banana (Musa sapientum L.)	Durian (Durio zibethinus)
Cashew apple (Anacardium occidentale)	Mangifera species
	Wine

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated

database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Pre-registered for 2009; no dossier available as of 12/09/21.

10. Conclusion

The maximum acceptable concentrations^a in finished products for propyl isovalerate are detailed below.

IFRA Category ^b	Description of Product Type	Maximum Acceptable Concentrations ^a in Finished Products (%) ^c
1	Products applied to the lips (lipstick)	0.54
2	Products applied to the axillae	0.16
3	Products applied to the face/body using fingertips	2.0
4	Products related to fine fragrances	3.0
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.76
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.76
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.76
5D	Baby cream, oil, talc	0.25
6	Products with oral and lip exposure	1.8
7	Products applied to the hair with some hand contact	6.1
8	Products with significant anogenital exposure (tampon)	0.25
9	Products with body and hand exposure, primarily rinse-off (bar soap)	5.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.98
10B	Aerosol air freshener	7.8
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.25
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No restriction

Note: ^aMaximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For propyl isovalerate, the basis was the subchronic reference dose of 3.33 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 7000 µg/cm².

^bFor a description of the categories, refer to the IFRA RIFM Information Booklet (<https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf>; December 2019).

^cCalculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, propyl isovalerate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Propyl isovalerate was assessed in the Blue-Screen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic

activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic and clastogenic activity of propyl isovalerate; however, read-across can be made to ethyl 2-methylbutyrate (CAS # 7452-79-1; see Section VI).

The mutagenic activity of ethyl 2-methylbutyrate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with ethyl 2-methylbutyrate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 µg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2000a). Under the conditions of the study, ethyl 2-methylbutyrate was not mutagenic in the Ames test, and this can be extended to propyl isovalerate.

The clastogenic activity of ethyl 2-methylbutyrate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with ethyl 2-methylbutyrate in DMSO at concentrations up to 1300 µg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1300 µg/mL in the presence and absence of metabolic activation. Ethyl 2-methylbutyrate did not induce binucleated cells with micronuclei when tested up to cytotoxic level or the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, ethyl 2-methylbutyrate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to propyl isovalerate.

Based on the data available, ethyl 2-methylbutyrate does not present a concern for genotoxic potential, and this can be extended to propyl isovalerate.

Additional References: RIFM, 1999.

Literature Search and Risk Assessment Completed On: 10/02/20.

11.1.2. Repeated dose toxicity

The MOE for propyl isovalerate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on ethyl 2-methylbutyrate. Read-across material ethyl 2-methylbutyrate (CAS # 7452-79-1; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In an OECD 422 combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 10 Sprague Dawley rats/sex/dose were administered ethyl 2-methylbutyrate via oral gavage at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil. Males were treated for 28–41 days, and females were treated for 40–51 days (maximum of 51 days, males and females). Males were euthanized on day 14 after mating and females (with offspring) were euthanized on day 5 postpartum, through subtotal exsanguination following anesthesia by isoflurane inhalation. No treatment-related adverse effects were reported for mortality, clinical signs, neurobehavior, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, pathological findings during necropsy, or histopathological examination. The NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the propyl isovalerate MOE for the repeated dose toxicity endpoint can be calculated by dividing the ethyl 2-methylbutyrate NOAEL in mg/kg/day by the total systemic exposure to Propyl isovalerate, 333/0.000064, or 5203125.

In addition, the total systemic exposure to propyl isovalerate (0.064 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Derivation of subchronic reference dose (RfD):

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a subchronic RfD of 3.33 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10×10), based on uncertainty factors applied for interspecies ($10 \times$) and intraspecies ($10 \times$) differences. The subchronic RfD for propyl isovalerate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, $100 = 3.33$ mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/01/20.

11.1.3. Reproductive toxicity

The MOE for propyl isovalerate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on propyl isovalerate. Read-across material ethyl 2-methylbutyrate (CAS # 7452-79-1; see Section VI) has sufficient data to support the reproductive toxicity endpoint. In an OECD 422 combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 10 Sprague Dawley rats/sex/dose were administered ethyl 2-methylbutyrate via oral gavage at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil. Males were treated for 28–41 days, and females were treated for 40–51 days (maximum of 51 days, males and females). Males were euthanized on day 14 after mating, and females (with offspring) were euthanized on day 5 postpartum. There were no treatment-related effects on mating performance, fertility, conception, gestation length, parturition, survival, litter size, or litter weight. In the F1 generation, no treatment-related effects were reported for mortality, clinical signs, body weight, and bodyweight changes during necropsy. Furthermore, no gross abnormalities were reported in pups. Therefore, the NOAEL for developmental toxicity and fertility was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013).

Therefore, the propyl isovalerate MOE for the reproductive toxicity endpoint can be calculated by dividing the ethyl 2-methylbutyrate NOAEL in mg/kg/day by the total systemic exposure to propyl isovalerate, $1000/0.000064$, or 19230769.

In addition, the total systemic exposure to propyl isovalerate (0.064 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes et al., 2007; Lauferweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/17/20.

11.1.4. Skin sensitization

Based on read-across hexyl 2-methylbutyrate (CAS # 10032-15-2), propyl isovalerate is considered a skin sensitizer with a defined NESIL of 7000 µg/cm².

11.1.4.1. Risk assessment. No data on skin sensitization studies are available for propyl isovalerate. Based on read-across material hexyl 2-methylbutyrate (CAS # 10032-15-2; see Section VI), propyl isovalerate is considered a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material, hexyl 2-methylbutyrate, was found to be negative in the *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens assay (RIFM, 2015b; RIFM, 2015a). In a murine local lymph node assay (LLNA), read-across material hexyl 2-methylbutyrate was found to be sensitizing with an EC3 value of 54.8% (13700 µg/cm²) (RIFM, 2000b). However, the results from this LLNA may be suboptimal since the test was conducted in the un-validated range (>25%) of the OECD guideline (Kolle et al., 2020). In a guinea pig open epicutaneous test (OET) on male and female guinea pigs, read-across material hexyl 2-methylbutyrate did not present reactions indicative of sensitization (Klecek, 1985). In a human maximization test, no skin sensitization reactions were observed with read-across material hexyl 2-methylbutyrate at 10% (6900 µg/cm²) in petrolatum (RIFM, 1977). Additionally, in Confirmation of No Induction in Humans tests (CNIHs) with read-across material hexyl 2-methylbutyrate at 7086 µg/cm² in 3:1 diethyl phthalate:EtOH or 967 µg/cm² in alcohol SDA 39C, no reactions indicative of sensitization was observed in any of the 109 (males and females over 18 years of age) or 38 volunteers (males and females), respectively (RIFM, 2018; RIFM, 1972).

Based on weight of evidence (WoE) from structural analysis and data on the read-across material hexyl 2-methylbutyrate, propyl isovalerate is a sensitizer with a WoE NESIL of 7000 µg/cm² (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a subchronic RfD of 3.33 mg/kg/day.

Additional References: Natsch et al., 2007; McKim et al., 2010.

Literature Search and Risk Assessment Completed On: 09/11/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, propyl isovalerate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for propyl isovalerate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, propyl isovalerate does not present a

concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol⁻¹ • cm⁻¹ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/01/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for propyl isovalerate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on propyl isovalerate. Based on the Creme RIFM Model, the inhalation exposure is 0.00096 mg/day. This exposure is 1458.3 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/16/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of propyl isovalerate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{ow}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, propyl isovalerate was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify propyl isovalerate as possibly persistent or bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent and bioaccumulative and toxic, or very persistent and very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥ 2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then

Table 1

Data summary for hexyl 2-methylbutyrate as read-across material for propyl isovalerate.

LLNA Weighted Mean EC3 Value µg/cm ² (No. Studies)	Potency Classification Based on Animal Data ^a	Human Data			
		NOEL-CNIH (Induction) µg/cm ²	NOEL-HMT (Induction) µg/cm ²	LOEL ^b (Induction) µg/cm ²	WoE NESIL ^c µg/cm ²
>13700 [1]	Weak	7086	6900	NA	7000

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

^a Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

^b Data derived from CNIH or HMT.

^c WoE NESIL limited to two significant figures.

performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Not applicable.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.4. Other available data

Propyl isovalerate was pre-registered for REACH with no additional information available at this time.

11.2.5. Risk assessment refinement

Not applicable.

Literature Search and Risk Assessment Completed On: 09/15/

20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** <https://echa.europa.eu/>
- **NTP:** <https://ntp.niehs.nih.gov/>
- **OECD Toolbox:** <https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm>
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2022.113120>.

Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{\max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with the *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

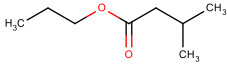
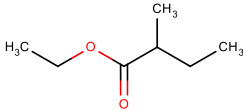
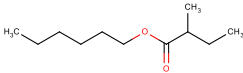
- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **National Library of Medicine's Toxicology Information Services:** <https://toxnet.nlm.nih.gov/>
- **IARC:** <https://monographs.iarc.fr>
- **OECD SIDS:** <https://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opthpv/public_search_publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** <https://www.google.com>
- **ChemIDplus:** <https://chem.nlm.nih.gov/chemidplus/>

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 12/09/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

	Target Material	Read-across Material	Read-across Material
Principal Name	Propyl isovalerate	Ethyl 2-methylbutyrate	Hexyl 2-methylbutyrate
CAS No.	557-00-6	7452-79-1	10032-15-2
Structure			
Similarity (Tanimoto Score)		0.71	0.69
Endpoint		<ul style="list-style-type: none"> • Genotoxicity • Repeated dose toxicity • Reproductive toxicity 	Skin sensitization
Molecular Formula	C ₈ H ₁₆ O ₂	C ₇ H ₁₄ O ₂	C ₁₁ H ₂₂ O ₂
Molecular Weight (g/mol)	144.21	130.19	186.29
Melting Point (°C, EPI Suite)	-43.92	-56.05	-9.14
Boiling Point (°C, EPI Suite)	155.90	134.87	218.34
Vapor Pressure (Pa @ 25°C, EPI Suite)	345.30	1070.58	19.07
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	356.70	1070.00	12.56
Log K_{OW}	2.76	2.26	4.23
Jmax (µg/cm²/h, SAM)	25.85	55.11	1.68
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	73.26	55.22	171.24
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found	
Carcinogenicity (ISS)	No alert found	Structural alert for nongenotoxic carcinogenicity Substituted n-alkylcarboxylic acids (Nongenotox)	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
In Vitro Mutagenicity (Ames, ISS)	No alert found	No alert found	
In Vivo Mutagenicity (Micronucleus, ISS)	No alert found	No alert found	
Oncologic Classification	Not classified	Not classified	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized	Urethane (Renal toxicity) Alert	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)	
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found		No alert found
Protein Binding (OECD)	No alert found		No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)		Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found		No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.		No skin sensitization reactivity domains alerts identified.
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on propyl isovalerate (CAS # 557-00-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical-chemical properties, and expert judgment, ethyl 2-methylbutyrate (CAS # 7452-79-1) and hexyl 2-methylbutyrate (CAS # 10032-15-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Ethyl 2-methylbutyrate (CAS # 7452-79-1) was used as a read-across analog for the target material propyl isovalerate (CAS # 557-00-6) for the genotoxicity, repeated dose toxicity, and reproductive toxicity endpoints.
 - o The target material and the read-across analog belong to the class of aliphatic esters.
 - o The key difference between the target material and the read-across analog is that target has a methyl substituent at the third position on the carboxylic acid end, whereas the read-across analog has a methyl substituent at the second position on the carboxylic end. Moreover, the target has a propyl substituent on the alcohol end, whereas the read-across analog has an ethyl substituent on the alcohol end. These structural differences are toxicologically insignificant.

- o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- o There is a structural alert for nongenotoxic carcinogenicity arising due to substituted n-alkylcarboxylic acids (carcinogenicity ISS) for the read-across analog. This is a typical structural alert for n-alkyl carboxylic acids. Substances belonging to this chemical class are potentially reactive as peroxisome proliferators (PPs). PPs are a diverse group of chemicals, including hypolipidemic drugs, plasticizers, and herbicides, that were found to cause liver cancer when chronically administered to rats and mice. These chemicals are considered nongenotoxic agents, given generally negative results in genotoxicity assays. The data on the read-across analog confirms that the substance does not pose a concern for genetic toxicity. Also, the structures of the read-across analog and the target material do not possess any reactive feature towards proteins or nucleic acids. Therefore, based on the data on the read-across analog and the structural similarity between the target substance and the read-across analog, the alerts are superseded by the data.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Hexyl 2-methylbutyrate (CAS # 10032-15-2) was used as a read-across analog for the target material propyl isovalerate (CAS # 557-00-6) for the skin sensitization endpoint.
 - o The target material and the read-across analog belong to the class of aliphatic esters.
 - o The key difference between the target material and the read-across analog is that the target material has a propyl substituent on the alcohol end, whereas the read-across analog has a hexyl substituent on the alcohol end. This structural difference is toxicologically insignificant.
 - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
 - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
 - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
 - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
 - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Research Institute for Fragrance Materials, Inc.

References

- Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. *Food Chem. Toxicol.* 82, S1–S19.
- Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. *Food Chem. Toxicol.* 47 (6), 1287–1295.
- Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. *Chem. Cent. J.* (4 Suppl. 1), S4.
- Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. *Regul. Toxicol. Pharmacol.* 72 (3), 660–672.
- Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. *Regul. Toxicol. Pharmacol.* 88, 144–156.
- ECHA, 2012. Guidance on information requirements and chemical safety assessment. November 2012 v2.1. <http://echa.europa.eu/>.
- ECHA, 2013. Ethyl 2-methylbutyrate registration dossier. Retrieved from. <https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/5861/1>.
- ECHA, 2017. Read-across assessment framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efe bd1851a.
- Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? *J. Photochem. Photobiol. B Biol.* 96 (1), 57–62.
- IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.
- Klecak, G., 1985. The Freund's complete adjuvant test and the open epicutaneous test. *Curr. Probl. Dermatol.* 14, 152–171.
- Kolle, S.N., Landsiedel, R., Natsch, A., 2020. Replacing the refinement for skin sensitization testing: considerations to the implementation of adverse outcome pathway (AOP)-based defined Approaches (DA) in OECD guidelines. [Supplementary table Attached]. *Regul. Toxicol. Pharmacol.* 115, 104713. August 2020.
- Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. *Food Chem. Toxicol.* 45 (12), 2533–2562.
- Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. *Regul. Toxicol. Pharmacol.* 62 (1), 160–182.
- McKim Jr., J.M., Keller III, D.J., Gorski, J.R., 2010. A new in vitro method for identifying chemical sensitizers combining peptide binding with ARE/EpRE-mediated gene expression in human skin cells. *Cutan. Ocul. Toxicol.* 29 (3), 171–192.
- Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. *Dermatitis* 32 (5), 339–352, 2021 Sep-Oct 01.
- Natsch, A., Gfeller, H., Rothaupt, M., Ellis, G., 2007. Utility and limitations of a peptide reactivity assay to predict fragrance allergens in vitro. *Toxicol. Vitro* 21 (7), 1220–1226.
- OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. <http://www.oecd.org/>.
- OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. <http://www.qsartoolbox.org/>.
- RIFM (Research Institute for Fragrance Materials, Inc.), 1972. Repeated Insult Patch Test with Hexyl 2-methylbutanoate. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 51907.
- RIFM (Research Institute for Fragrance Materials, Inc.), 1977. Report on Human Maximization Studies. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 1691.
- RIFM (Research Institute for Fragrance Materials, Inc.), 1999. Mutagenicity Evaluation of Ethyl-2-Methylbutyrate in the Ames Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan-Roure. RIFM report number 35741.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2000a. Mutagenicity Study of Ethyl 2-methylbutyrate (Ethylmethylbutyrate-2) in the Salmonella typhimurium/ mammalian Microsome Reverse Mutation Assay (Ames-Test). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 61535.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2000b. Hexyl 2-methylbutyrate (Cydrane): Local Lymph Node Assay in Mice (Identification of Contact Allergens). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 76691.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of Propyl Isovalerate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 66747.

- RIFM (Research Institute for Fragrance Materials, Inc.), 2014. Ethyl 2-methylbutyrate: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 68208.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2015a. Induction of Antioxidant-Response Element Dependent Gene Activity Cytotoxicity (Using MTT) in the Keratinocyte ARE- Reporter Cell Line Keratinosens. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 69647.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2015b. Direct Peptide Reactivity Assay (DPRA) of Alpha-Amylcinnamyl Alcohol, Benzyl Cinnamate, Butyl Acrylate, P-Tert-Butyldihydrocinnamaldehyde, Carvone and 1-cyclohexylethyl 2-butenate. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 69649.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Hexyl 2-methylbutyrate: Repeated Insult Patch Test (RIPT). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 73721.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2020a. Clustering a Chemical Inventory for Safety Assessment of Fragrance Ingredients: Identifying Read-Across Analogs to Address Data Gaps. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76272.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2020b. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76775.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2021. Exposure Survey 30, January 2021.
- Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. *Chem. Res. Toxicol.* 20 (7), 1019–1030.
- Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. *J. Chem. Inf. Model.* 50 (5), 742–754.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. *Regul. Toxicol. Pharmacol.* 72, 673–682.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. *Regul. Toxicol. Pharmacol.* 86, 148–156.
- Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. *Environ. Toxicol. Chem.* 21 (6), 1301–1308.
- Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. *Regul. Toxicol. Pharmacol.* 72 (3), 586–601.
- Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. *Food Chem. Toxicol.* 74, 164–176.
- US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
- US EPA, 2012b. The ECOSAR (ECOLOGical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.